IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2174
FERNANDEZ, et al.,	Art Unit: 1652
Appl. No. 10/003,021	Examiner: Fronda, C.
Filed: November 14, 2001	Atty. Docket: IVGN 276.1 CON
For: **Libraries of Expressible Gene Sequences**	

Amended Appeal Brief in Response to the Notice of Non-Compliant Appeal Brief Under 37 CFR 41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In reply to the Notice of Non-Compliant Appeal Brief dated **May 18, 2007**, Applicants submit herewith the Appeal Brief that was previously filed on April 2, 2007, which has been amended to identify the claims on appeal.

It is not believed that extensions of time or fees are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional fees are due, or if additional extensions of time are necessary to prevent

abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required are hereby authorized to be charged to our Deposit Account No. 50-3994.

Respectfully submitted,

Date: May 31, 2007

/Natalie A. Davis/
Natalie A. Davis
Reg. No. 53,849
Agent for Appellants

Invitrogen Corp.
1600 Faraday Ave.
Carlsbad, CA 92008
(760) 268-7469

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Brief on Appeal Under 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

A Notice of Appeal from the final rejection of claims 41-43 and 45-58 was filed on February 1, 2007. Appellants hereby file this Appeal Brief, together with the required brief filing fee under § 41.20(b)(2) of $500.00.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 50-3994.

Table of Contents

I. Real Party In Interest

The real party in interest in this appeal is Invitrogen Corporation.

II. Related Appeals and Interferences

No other prior or pending appeals, interferences or judicial proceedings are known to the Appellants, the Appellants' legal representative, or assignee which may be related to, or directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 41-43 and 45-58 are on appeal.

Claims 1-40, 44, and 59-66 have been canceled.

Claims 41-43 and 45-58 are rejected.

IV. Status of Amendments

No amendments were filed subsequent to the final rejection.

V. Summary of Claimed Subject Matter

Claims 41 and 58 are the independent claims involved in this Appeal. The invention defined by claim 41 relates generally to isolated expression vectors. The

expression vector comprises a 5'-CACC sequence linked immediately 5' to a start codon of an open reading frame (ORF). The ORF is linked in-frame to a polynucleotide encoding a heterologous peptide, thereby encoding a fusion protein comprising the ORF-encoded polypeptide and the heterologous peptide. Support for claim 41 can be found throughout the specification, for example, at page 2, lines 1-6 and lines 13-27 through page 4, line 22; page 7, line 26 through page 8, line 27; page 10, lines 7-17; page 12, line 26 through page 13, line 4; Example 1 at pages 8-21; Example 2 at page 78, line 3 through page 79, line 19; Table 1 at pages 21-78; Table 2 at pages 79-146; and Example 3 at pages 147-148.

Claim 58 relates generally to libraries of expression vectors. The libraries comprise a plurality of expression vectors, where each vector comprises a 5'-CACC sequence linked immediately 5' to a start codon of an open reading frame (ORF). The ORF is linked in-frame to the polynucleotide encoding a heterologous peptide, thereby encoding a fusion protein comprising the ORF-encoded polypeptide and the heterologous peptide. The ORF of an expression vector in the plurality may be the same or different from open reading frames of other expression vectors in the plurality. Support for claim 58 can be found throughout the specification, for example, at page 2, lines 1-6 and 13-27 through page 4, line 22; page 7, line 26 through page 8, line 27; page 10, lines 7-17; page 12, line 26 through page 13, line 4; Example 1 at pages 8-21; Example 2 at page 78, line 3 through page 79, line 19; Table 1 at pages 21-78; Table 2 at pages 79-146; and Example 3 at pages 147-148.

VI. Grounds of Rejection to be Reviewed on Appeal

Claims 41-43 and 45-58 stand rejected under 35 U.S.C. 103(a), as being unpatentably obvious over Dubensky, et al., (U.S. Pat. No. 6,342,372), in view of Guan, et al., (EP Pat. No. 0286239B1) and Gregoire, et al., (*J. Biol Chem.,* 1996, Dec 20; 271(51):32951-9).

VII. Argument

A. Legal Standard for Obviousness

Establishing prima facie obviousness requires a showing that each claim element is taught or suggested by the prior art. See *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Absent a showing of such motivation and suggestion, prima facie obviousness is not established. See *In re Fine*, 837 F.2d 1071 (Fed Cir 1988). The Court of Appeals for the Federal Circuit has indicated that:

> The PTO has the burden under section 103 to establish a prima facie case of obviousness…It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. Id at 1074.

To meet its burden, the PTO "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." Id. at 1075. The Court of Appeals for the Federal Circuit has held numerous times that such hindsight analysis is impermissible. Instead, the PTO must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited

references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 f.2d 1132, 1143 (Fed. Cir. 1985).

Further, the PTO must consider prior art references in their entirety, *i.e.* as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The Court of Appeals for the Federal Circuit has instructed that "references that teach away cannot serve to create a prima facie case of obviousness" (*In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)), and that an "applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect" (*In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997)).

1. The Cited References

a. The Dubensky Reference

The Dubensky reference discloses eukaryotic vector systems for the production of recombinant proteins, where the vectors include a CACC sequence linked 5' to the ATG start codon of a nucleic acid encoding a heterologous polypeptide. The disclosed vectors are configured in a "bicistronic heterologous configuration" specifically designed to prevent the expression of fusion proteins. This is because heterologous genes in Dubensky's bicistronic vectors are separated by a stop codon so that the encoded proteins are expressed separately. See column 90, paragraphs 2 and 3.

The Dubensky reference does not disclose expression vectors having an open reading frame (ORF) linked in-frame to a polynucleotide encoding a heterologous peptide, thereby encoding a fusion protein comprising the ORF-encoded polypeptide and the heterologous peptide. Rather heterologous proteins encoded by Dubensky's bicistronic vectors are expressed separately and are not associated as a fusion protein.

b. The Guan Reference

The Guan reference discloses vectors that encode fusion proteins; specifically polypeptides linked to maltose binding protein. See column 1, lines 1-14; column 3, line 53 through column 4 line 3; and column 5, line 55 through column 6, line 18. The disclosed fusion protein is purified by affinity chromatography using the maltose binding protein. See column 1, lines 13-18 and column 12, lines 40-52.

The Guan reference does not disclose an isolated expression vector comprising the sequence 5'-CACC linked immediately 5' to a start codon of an open reading frame or an expression library comprising such vectors.

c. The Gregoire Reference

The Gregoire reference discloses a vector that encodes a fusion protein; specifically a recombinant form of the horse allergen Equ c1 protein linked to a polyhistidine tail. The disclosed fusion protein is purified by affinity chromatography using the polyhistidine tail. See the abstract; page 32951, column 2, third paragraph; figure 1 on page 32952; and figure 2 on page 32954 and column 1, third paragraph.

The Gregoire reference does not disclose an isolated expression vector comprising the sequence 5'-CACC linked immediately 5' to a start codon of an open reading frame or a fusion protein or an expression library comprising such vectors.

2. The Examiner's Position

The Examiner argues that the methods of claims 41-43 and 45-58 are obvious over Dubensky in view of Guan and Gregoire.

The Examiner states that the Dubensky reference teaches an oligonucleotide primer comprising a CACC sequence linked 5' to the ATG start codon of a nucleic acid encoding a heterologous polypeptide. The Examiner recognizes that Dubensky does not disclose expression vectors having an open reading frame (ORF) linked in-frame to a polynucleotide encoding a heterologous peptide thereby encoding a fusion protein comprising the ORF-encoded polypeptide and the heterologous peptide. The Examiner offers the Guan and Gregorie references to cure this deficiency.

The Guan and Gregorie references are offered to address the shortcomings of Dubensky: an open reading frame (ORF) that is linked in-frame to a polynucleotide encoding a heterologous peptide, thus encoding a fusion protein comprising the ORF-encoded polypeptide and the heterologous peptide. Specifically, the Guan reference is offered for its disclosure of polypeptides linked to a maltose binding protein. The Gregorie is offered to specifically address Dubenskys' shortcoming of an affinity purification tag, which is required by claims 45 and 46. The Gregorie reference is said to disclose a recombinant protein with a polyhistidine tail.

As to motivation to combine these references, the Examiner simply states that it would have been obvious to a skilled artisan to modify Dubenskys' bicistronic expression vectors in the manner disclosed by Guan, to produce fusion proteins suitable for purification. The Examiner further states that it would have been obvious to further modify Dubensky's polynucleotide to encode a polyhistidine tail as disclosed in Gregorie. Specifically, the Examiner states:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide comprising the CACC sequence (SEQ ID No. 69) linked to the 5' start codon ATG of nucleic acids encoding heterologous peptides taught by Dubensky Jr. et al. such that the DNA encoding the MBP and DNA encoding a peptide that can be recognized and cut by a protease as taught by Guan et al. is linked to the polynucleotide taught by Dubensky Jr. et al. Alternatively, the polynucleotide taught by Dubensky Jr. et al. is modified to have a DNA encoding a polyhistidine tail as taught by Gregorie et al. See Office Action dated August 1, 2006 at page 3.

3. The Appellant's Position

Claims 41-43 and 45-58 are not obvious over the cited references.

Claims 41-43 and 45 are drawn to isolated expression vector, comprising (1) the sequence 5'-CACC linked immediately 5' to a start codon of (2) an open reading frame (ORF) linked in-frame to a polynucleotide encoding a heterologous peptide, thereby encoding a fusion protein comprising the ORF-encoded polypeptide and the heterologous peptide. Claim 58 is drawn to libraries of such isolated expression vectors.

The Examiner appears to be relying on hindsight in combining the Dubensky, Guan and Gregoire references in arriving at an obviousness determination. Worse, in so doing, the Examiner has failed to consider the cited references in their entirety, including the parts that teach away from the claimed invention.

The Examiner has ignored the fact that Dubensky's vectors are configured in a "bicistronic heterologous configuration" specifically designed to prevent the expression of fusion proteins. Applicants have brought this fact to the Examiner's attention in response to the Office Actions dated October 19, 2005 and August 1, 2006. Dubensky's bicistronic vectors include a stop codon between heterologous genes, and therefore are suitable only for the expression of single peptides. See column 90, paragraphs 2 and 3. Dubensky's bicistronic vectors are specifically designed not to (and cannot) encode fusion proteins as required by the present claims.

The Examiner's selective reading of Dubensky is contrary to the proscription of the Court of Appeals for the Federal Circuit – references that teach away cannot serve to create a prima facie case of obviousness. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Moreover, ignoring a key aspect of the Dubensky disclosure to focus only on claim elements that are disclosed, and combining those with the remaining elements found in other references is not appropriate – it is a clear example of impermissible hindsight analysis.

The Examiner has not provided any "suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention," as required by the Court of Appeals for the Federal Circuit.

See *In re Fine* at 1071. Applicants therefore respectfully request that this rejection under 35 U.S.C. § 103 be withdrawn.

D. Conclusion

In view of the forgoing discussion, Appellants respectfully submit that the subject matter defined by claims 41-43 and 45-58 are patentable over the cited art. Appellants therefore respectfully request that the Board reverses the Examiner's final rejection of the pending claims and remand this application for issue.

Respectfully submitted,

Date: May 31, 2007

/Natalie A. Davis/
Natalie A. Davis
Reg. No. 53,849
Agent for Appellants

Invitrogen Corp.
1600 Faraday Ave.
Carlsbad, CA 92008
(760) 268-7469

VIII. Claims Appendix

41. An isolated expression vector, comprising the sequence 5'-CACC linked immediately 5' to a start codon of an open reading frame (ORF), wherein the ORF is linked in-frame to a polynucleotide encoding a heterologous peptide, thereby encoding a fusion protein comprising a polypeptide encoded by the ORF and the heterologous peptide.

42. The expression vector of claim 41, wherein the ORF encodes a full length polypeptide.

43. The expression vector of claim 41, wherein the ORF lacks a stop codon.

45. The expression vector of claim 41, wherein the heterologous peptide comprises an affinity purification tag or an epitope tag.

46. The expression vector of claim 41, wherein the heterologous peptide comprises a polyhistidine tag, a chitin binding domain, glutathione-S-transferase, biotin, or a V5 epitope.

47. The expression vector of claim 41, further comprising a polynucleotide encoding an endopeptidase recognition sequence linked in-frame between the ORF and the polynucleotide encoding the heterologous peptide.

48. The expression vector of claim 41, which is a eukaryotic expression vector or a prokaryotic expression vector.

49. The expression vector of claim 41, which is suitable for prokaryotic expression and eukaryotic expression.

50. The expression vector of claim 41, which is suitable for expression in bacteria cells, fungi, insect cells, yeast cells, plant cells, or mammalian cells.

51. The expression vector of claim 41, further comprising a promoter, an enhancer sequence, a selection marker sequence, an origin of replication, an epitope-tag encoding sequence, an affinity purification-tag encoding sequence, or a combination thereof.

52. The expression vector of claim 51, wherein the promoter is a constitutive promoter or an inducible promoter.

53. The expression vector of claim 52, wherein the constitutive promoter is a T7 promoter, a β-lactamase gene promoter, a bacteriophage λ int promoter; a chloramphenicol acetyl transferase gene promoter, an SV40 promoter, an RSV promoter or a CMV promoter.

54. The expression vector of claim 52, wherein the inducible promoter is a trp promoter, a recA promoter, a lacZ promoter, a lacI promoter, an araC promoter, an I-amylase promoter, a metallothionein I gene promoter, a herpesvirus TK promoter, an SV40 early promoter, a yeast gal1 gene promoter, an EF1 promoter, or an ecdysone-responsive promoter.

55. The expression vector of claim 51, wherein the selection marker confers resistance to ampicillin, tetracycline, kanamycin, bleomycin, streptomycin, hygromycin, neomycin, or Zeocin™ antibiotic.

56. The expression vector of claim 51, wherein the selection marker is a hisD gene sequence or a URA3 sequence.

57. The expression vector of claim 51, wherein the origin of replication (ori) is an *Escherichia coli* oriC ori, a yeast 2μ ori, a yeast ARS ori, and sf1 ori, or an SV40 ori.

58. A library of expression vectors, comprising a plurality of expression vectors, wherein each expression vector comprises the sequence 5'-CACC linked immediately 5' to a start codon of an open reading frame (ORF), wherein said ORF is linked in-frame to a polynucleotide encoding a heterologous peptide, thereby encoding a fusion protein comprising a polypeptide encoded by the ORF and the heterologous peptide, and wherein an ORF of an expression vector in the plurality is the same or different from open reading frames of other expression vectors in the plurality.

IX. Evidence Appendix

Exhibit	Title of Exhibit	Location in Record
Exhibit 1	Dubensky, et al., U.S. Pat. No. 6,342,372	Cited by Examiner in Office Action dated August 1, 2006
Exhibit 2	Guan, et al., EP Pat. No. 0286239B1	Cited by Examiner in Office Action dated August 1, 2006
Exhibit 3	Gregoire, et al., (*J. Biol Chem.,* 1996, Dec 20; 271(51):32951-9)	Cited by Examiner in Office Action dated August 1, 2006

X. Related Proceedings Appendix

None.